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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,445	HOUGHTON, PETER J.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Dec. 15, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. Claims 1-26 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling the treatment of neuroblastoma, glioblastoma and rhabdomyosarcoma, does not reasonably provide enablement for the treatment of all types of cancer using the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment(s)

The following is responsive to Applicant's amendment received Dec. 15, 2004.

No claims are cancelled. No new claims are added. Claims 1-26 are currently pending.

The previous objection of claim 25, set forth in paragraph 1 of the office action mailed June 17, 2004 is withdrawn in view of Applicant's amendment and the remarks contained therein.

However, Applicant's arguments traversing the previous claim rejection under 35 USC 112, first paragraph, set forth in paragraphs 1-2 of the office action mailed June 17, 2004 have been considered but are not found to be persuasive.

Said rejection is maintained essentially for the reasons given previously in the office action mailed June 17, 2004 with the following additional comment(s) set forth below.

Applicant's arguments traversing the previous claim rejection under 35 USC 103(a) set forth in paragraphs 3-4 of the office action mailed June 17, 2004 have been carefully considered but are moot in view of the following new ground(s) of rejection. Said rejection under 35 USC 103(a) is withdrawn in favor of the following new ground(s) of rejection.

Claim Rejection—35 USC 112, paragraph 1:

Applicant contends that per the Wands factors, applicant has enabled the claims to treat cancer. Specifically Applicant argues

With regard to the state of the prior art, applicant respectfully notes that the general knowledge in the art recognizes the utility of temozolomide and irinotecan for numerous types of cancers (see generally cited art on first page of applicants specifIcation). Further. while the Examiner points out specific references stating that these compounds are effective against certain types of cancers, applicant respectfully points that even the Burton reference cited by the Examiner notes that temozolomIde acts generally with an anti-tumor effect by methylation of tumor DNA, while irinotecan acts by inhibiting topoisomerase I, an enzyme that normally functions to relieve torsional strain caused by the synthesis of new strands of DNA or RNA around a double helix (see Burton. page 3, middle two paragraphs). Applicant respectfully suggests that cancers other than those specified by the Examiner can be treated by these compounds due to general cyotoxic chemotherapeutic action they inflict on tumor DNA. Therefore, these compounds are enabled by the art and the specification to treat cancer. In support of thIs, applicants refer the Examiner to the references clted on page 1 of the specification. Copies of these references have been provided to the Examiner in an IDS filed on May 21, 2003. Applicant suggests that the examples provided in the specification on pages 7-24, in addition to the general knowledge in the art, provide a sufficient road map to one of ordinary skill in the art to prevent anyone from being unduly burdened from experimenting with the claimed invention.

Said arguments have been considered but are not found to be persuasive.

The references referred to at page 1 of the specification do not recognize the ability of temozolomide or irinotecan to treat all kinds of cancer. The cited journal articles at page 1 of applicant's specification discuss temozolomide's activity against

melanoma. Furthermore, Applicant admits on page 1, lines 14-15 that temozolomide is not always effective and has dose-limiting side effects. According to MPEP 2164.08, The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. > AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003);< In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). See also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003).

In this case, the Examiner respectfully submits that the scope of enablement in the disclosure does not bear a "reasonable correlation" to the scope of the claims. As discussed in the office action mailed June 17, 2004, cancer is a broad term, which encompasses a vast number of cancer types, each involving different types of tissues and organs as well as blood borne-cancers. The art has yet to recognize treatment of all types of cancers using one combination of drugs. Thus given the state of the art as set

forth in the office action as well as page 1 of applicant's specification, the artisan is currently unaware of any one particular combination of anticancer agents that is effective against all cancer cell types. In fact the state of the art demonstrates the unpredictability of treating cancer. The court has held "cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." Please see In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

Applicant's specification is not enabled for the treatment of all cancer cell types. Data from working examples that relate to only a few cancer cell types does not reasonably correlate to the scope of the claims. The scope of enablement provided to one of ordinary skill in the art by Applicant's disclosure is not commensurate with the scope of protection sought by Applicant's claims. Therefore, the examiner respectfully maintains that one of ordinary skill in the art would be burdened with undue experimentation to practice the full scope of the claimed method, which involves treatment of all kinds of cancers.

Therefore, the rejection is respectfully maintained.

New Ground(s) of Rejection

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al. and Ragab 6,346,524 (submitted by Applicant) in view of Friedman 6,251,886.

Burton et al. discuss new chemotherapy options for patients suffering from malignant gliomas. Two new drugs, temozolomide and irinotecan have shown promise in the treatment of patients who have malignant gliomas. Temozolomide is an oral pharmaceutical agent that has shown good responses in patients during Phase II studies. Please see page 159, Cytotoxic chemotherapy, first full paragraph.

Irinotecan is an intravenous drug that has previously been used in the treatment of colon cancer. Burton et al. teach that, as a single agent, irinotecan demonstrated a good response with malignant gliomas. In one study 60 patients with recurrent malignant gliomas were treated with a 125 mg/m^2 dose weekly for 4 weeks, followed by a 2 week period of rest. Please see page 159, Cytotoxic chemotherapy, second full paragraph.

Ragab disclose a method of treating a patient suffering from cancer by administering an effective amount (40-150 mg/m^2/day) of temozolomide for a dosing period of from 5 to 25 days. Ragab also discloses that treatment cycles may continue for as long as needed to cure or eliminate the cancer that is being treated. Please see the abstract; col. 2, lines 31-47.

Burton and Ragab do not specifically disclose treatment methods involving a combination of temozolomide and irinotecan. Yet, the Examiner refers to Friedman, which teaches a method for treating cancer (gliomas, melanomas, carcinomas, sarcoma, leukemia etc.) by administering an effective amount of temozolomide. Please see the abstract; col. 10, lines 35-65. Friedman additionally discloses that temozolomide may administered in combination with other chemotherapeutic agents such as irinotecan. Please see col. 13, lines 1-5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Burton et al. and Ragab to treat malignant gliomas using a combination of temozolomide and irinotecan because one of ordinary skill in the art would reasonably expect the additive effect of temozolomide and irinotecan to be effective in treating malignant gliomas. Such a modification would have been motivated by the reasonable expectation that the combination of the two chemotherapeutic drugs would effectively treat patients suffering from malignant gliomas.

With respect to the claimed dosage amounts of temozolomide and irinotecan, since the anti-tumor effect of these drugs is dependent upon dosage amounts, it would have been obvious to one of ordinary skill in the art to further modify the dosage amounts in

the prior art such that temozolomide and irinotecan are administered in an amount that is effective to optimize treatment of malignant gliomas.

Finally, with respect to the claimed dosing schedule, since Burton et al. establish a preferred dosing schedule at least for irinotecan, it would have been obvious to one of ordinary skill in the art to further modify dosing schedules such that the overall combination of temozolomide and irinotecan is effective in treating the patients suffering from malignant gliomas.

3. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al. and Ragab, supra in view of Friedman, supra.

Burton as applied above.

Ragab as applied above. In addition, Ragab discloses a medical kit containing temozolomide and printed instructions for administering the drug to a cancer patient. Please see the abstract; col. 3, lines 19-30.

Burton et al. and Ragab do not specifically disclose a medical kit containing a combination of temozolomide and irinotecan along with printed instructions for administration to a cancer patient. Yet, the Examiner refers to Friedman, which teaches a method for treating cancer (gliomas, melanomas, carcinomas, sarcoma, leukemia etc.) by administering an effective amount of temozolomide. Please see the abstract; col. 10, lines 35-65. Friedman additionally discloses that temozolomide may administered in combination with other chemotherapeutic agents such as irinotecan. Please see col. 13, lines 1-5.

It would have been obvious to one of ordinary skill in the art at the time the

invention was made to modify the compositions of Burton and Ragab to form a kit containing a combination of temozolomide and irinotecan because one of ordinary skill in the art would reasonably expect the resulting medical kit to be economically feasible, convenient thus ensuring patient compliance.

With respect to the printed instructions for use, since the printed instructions relate to the intended use of the product and do not further define the product structurally or chemically, it does render the claimed combination unobvious. Furthermore, the court in In re Ngai et al. states that "where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." Please see In re Ngai et al., 70 USPQ2d 1862 (CAFC 2004) (affirming In re Gulack, 703 F.2d 1381 (Fed. Cir. 1983)). In this case, the printed instructions do not depend on the medical kit and the medical kit does not depend on the printed instructions. The ultimate function of the medical kit does not rely on the instructions but on the active pharmaceutical agents, i.e. temozolomide and irinotecan.

Conclusion

Claims 1-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
April 5, 2005

Cybille Delacroix-Muirheid
Patent Examiner Group 1600